#17 Pre Response 9/30/03

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No. 065691-0193

In re patent application of

Abdessatar (Sami) CHTOUROU et al. Group Art Unit: 1653

Serial No. 09/581,398 Examiner: Abdel A. Mohamed

Filed: August 3, 2000

For: METHOD OF FILTERING VIRUSES FROM A FACTOR VIII SOLUTION

PRELIMINARY REMARKS

Mail Stop RCE
Commissioner for Patents
Washington, D.C. 20231

Sir:

Attached hereto is a declaration by one of the inventors, Dr. Abdessatar Chtourou. Dr. Chtourou's declaration clarifies that one of ordinary skill in the art would have not been motivated to arrive at the present invention in light of WO 96/00237. As Dr. Chtourou states, the factor VIII of the WO 96/00237 application was a recombinant factor VIII, aka r-VIII SQ, in which domain B has been deleted. (See WO '237, page 5, bottom). When domain B is removed from factor VIII, the molecular weight of the molecule drops from 290 kDa to 170 kDa. As stated in WO 96/00237, a Viresolve™/180 filter was taught as being suitable for filtering r-VIII SQ, because this recombinant protein has a molecular weight of about 170kDa. (See *id.*, page 8, lines 19-20.) This does not suggest that a smaller 15 filter can be used to effectively filter a natural factor VIII molecule of 170 kDa. Therefore, the present invention, which is capable of using a 15 filter to filter a natural factor VIII molecule, is not suggested by WO 96/00237 or any of the other cited references.

It is respectfully submitted that this application is in condition for allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to telephone the undersigned at the number listed below if the Examiner believes such would be helpful in advancing the application to issue.

Serial No. 09/581,398 Attorney Docket No. 065691/0193

If any additional extension(s) of time are required for the filing of this paper, applicants expressly petition for such extension(s) and authorize the Commissioner to charge any deficiency to Deposit Account 19-0741.

Respectfully submitted,

May 12, 2003
Date

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Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Commissioner is hereby authorized to charge Deposit Account No. 19-0741 for any such fees; and applicants hereby petition for any needed extension of time.

THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Appln of:

Serial N° 98/581,398 Group Art Unit: 1653

Filed on 08/03/2000 Examiner: MOHAMED ABDEL A

DECLARATION UNDER 37 CFR§ 1.132

Honorable commission of Patent and Trademarks
Washington, DC 20231

Sir :

I, CHTOUROU,A. S. declare as follow :

1. That I have a Doctorate degree in industrial Biochemistry Sciences (1984)

2. That my professional career was as follows :

PROFESSIONAL CONTACT INFORMATION

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PROFESSIONAL EXPERIENCE

May 1997-present **Director, Pre-clinical Development**
LFB, Les Ulis, France

March 94-May 97	**Head of Plasma Protein Research and Development Department** LFB, Les Ulis, France
May 87- March 94	**Project Leader** **Head of FVIII Process Development and Characterization Laboratory** FNTS, Les Ulis, France
January 85- May 87	**Scientific and Technical Specialist** **Assistant Manager of the Technical and Scientific Department** Pharmacia France, Biotechnology Division, Bois-d'Arcy, France
1984-1985	**Research Fellow,** *Laboratoire d'Ecologie Microbienne* INRA (National Institute of Agronomic Research), Jouy-en-Josas, France
1980-1984	**Pre-doctoral Research,** *Laboratoire de Biochimie et de Technologies Laitières,* INRA, Jouy-en-Josas, France
1979-1980	**High School Teacher** Institut du Châtelet, Paris, France

EDUCATION

1984	**Doctorate in Biochemistry** Universités Paris VII, Paris XI, ENSIA
1980	**Master of Science in Biochemistry** Université Paris VII
1979	**Bachelor of Science in Biochemistry** Université Paris VII

3. That I am well aware of the contents of the present application as I am the inventor of it. I read and understood the official action dated 02/19/2003.

I Submit that :

Factor VIII is a blood plasma glycoprotein of about 290 kDa. Analysis of the deduced primary amino acid sequence of human FVIII determined from the cloned cDNA indicates that it is a heterodimer processed from a larger precursor polypeptide. The heterodimer consists of a C-terminal light chain of about 80 kDa in a metal ion-dependent association with an about 210 kDa N-terminal heavy chain fragment. The amino acid sequence of FVIII is organized into three structural domains: a triplicated A domain of 330 amino acids, a single B domain of 980 amino acids, and a duplicated C domain of 150 amino acids. The B domain is not critical to the biological activity of the macromolecule.

Indeed, recently deleted factor VIII cDNA molecules coding for recombinant factor VIII derivatives have been developed. The designed B domain deleted factor VIII derived from a full-length factor VIII cDNA, that, when expressed in animal cells, produced high levels of a factor VIII-like protein with factor VIII activity. The protein consisted essentially of two polypeptide chains derived from human factor VIII, the chains having molecular weights of 90 kDa and 80 kDa, respectively. This polypeptide sequence is commercially known as rFVIII-SQ or REFACTO.

The main differences between the natural plasma derived FVIII and the B domain deleted recombinant one is related to their respective molecular weights i.e. 290 kDa versus 170 kDa .

It is also important to remind that Factor VIII circulates as an inactive precursor in blood, bound tightly and non-covalently to von Willebrand factor (vWF). vWF is a glycoprotein which is formed in various cells of the human body and later is liberated into the circulation. At this, a vWF dimer (primary vWF dimer) having-a molecular weight of approximately 450

kDa is synthesized in the cells, starting from a polypeptide chain having a molecular weight of approximately 225 kDa (vWF monomer) by forming several sulfur bonds. From the vWF dimers, further polymers of vWF with ever increasing molecular weights, up to approximately 20000 kDa, are in turn formed by forming links via sulfur bonds.

Thus, the FVIII-vWF complexes molecular weights may varies from 730 kDA to 20000 kDa. This is far larger than the 170 kDa of the recombinant **FVIII SQ** mentioned in WO96 / 00237 and **It is also far larger than the nominal pore size of VIRESOLVE 180 membrane.**

The filtration of the FVIII SQ using a 180 kDa cut off membrane might be foreseen as feasible since the protein molecular weight is smaller than membrane nominal pore size. This is not the case for either the natural FVIII nor the FVIII-vWF complexes.

On the faith of what I explained in supra, I declare that the prior art disclosed in WO96 / 00237 patent application couldn't allow to foresee the filtration of the natural FVIII on 15nm, which is the subject-matter of the claims. Furthermore, we discovered optimal operating conditions for filtering on 15nm such as:

- Presence of CaCl2 (claim 28)
- Filtration with low pressure (< 0,3 bar)-claim 33
- Filtration at 35°C ± 5°C (claim 35)

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements and the like so made are punishable by fine and imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted

Date : 04/25/03

By : Chtourou A. Sy